### Important factors to consider when validating and qualifying imaging biomarkers (BMs)

<table>
<thead>
<tr>
<th>Attribute of imaging BM</th>
<th>Impact on technical validation</th>
<th>Impact on biological validation</th>
<th>Impact on economic viability</th>
<th>Biospecimen BM comparison</th>
<th>Imaging BM problems and solutions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Imaging devices, agents and software</td>
<td>Validation required for all sites</td>
<td>None, if technical validation is performed correctly</td>
<td>Unable to ensure most cost-effective BM acquisition (choices limited)</td>
<td>Biospecimen BMs are analyzed using one (or a few identical) in vitro diagnostic devices</td>
<td>Many imaging BMs (e.g. ADC, Ktrans) give numerically different values on different scanners. Use of phantoms - exhaustive exercises needed to standardize (e.g. AJCC on staging, RECIST on response, QuIC-ConCePT). Development of appropriate phantoms where lacking at present.</td>
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<tr>
<td>Different imaging devices from different vendors are installed in different hospitals</td>
<td>Important factors affecting technical validation may be proprietary, obscure, and may change unexpectedly</td>
<td>None, if technical validation is performed correctly</td>
<td>-</td>
<td>In vitro diagnostic devices are designed, maintained and approved for specific purpose of measuring the biospecimen BM – this substantially reduces risk in technical validation. QIBA seeking regulatory approval for 'off label' BM such as ADC and Ktrans.</td>
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<td>Imaging devices may not be designed, maintained or approved for the purpose of measuring the BM</td>
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<td>-</td>
<td>Parallel imaging changes noise characteristics and may affect measurement (e.g. ADC). Gradient improvements affect ADC. Check effect of innovation on BM against existing systems.</td>
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<tr>
<td>Innovation in imaging devices driven by competition to improve picture quality; has unpredictable effect on BM measurement</td>
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<td>Examples of 'Sinerem', gadofosveset, and many PET tracers.</td>
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<td>Imaging contrast agent or tracer may not be designed, maintained or approved for the purpose of measuring the BM</td>
<td>Withdrawal of agent in some markets, or failure to develop in certain markets severely limits availability</td>
<td>-</td>
<td>Priced for radiologic diagnosis not for BM use</td>
<td>Biospecimen BMs rarely require administration of a drug substance to the patient</td>
<td>Can hinder direct comparison between different centres. Central analysis hubs for multicentre studies. Use of phantoms to standardize. Need for CE style approval of software.</td>
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<tr>
<td>Non-proprietary software used for many imaging BM</td>
<td>Validation required for each software version</td>
<td>May influence biological meaning for BM</td>
<td>May require patented software for translation across second ‘Cooksey’ translational gap</td>
<td>Biospecimen BMs have stable platform due to regulatory approval</td>
<td>Can affect radiologic diagnosis of lesion, QuIC exercises needed to standardize (e.g. ADC). Validation required for each software version.</td>
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| 2. Resources and Staff | | | | | |
| Quality of the imaging BM data dependent on performance of radiologist and technician | Technical validation influenced by each operator | None, if technical validation is performed correctly | Can lead to increased cost from data exclusion. Significant ongoing cost for set up, training and retraining | Biospecimen BM acquisition is less complex than imaging BMs | Quality of lung/liver BMs may depend on control of motion. Some modalities are very user-dependent (e.g. ultrasound). Use highly trained staff, familiar with protocols. |
| BM measurement dictated by workflow in Radiology and Nuclear Medicine departments rather than patient or oncologist needs | May limit throughput and hence recruitment | - | Costs dictated by Radiology and Nuclear Medicine departments | Pathology and Clinical Chemistry departments can accommodate patient and oncologist needs | Ktrans vary with coffee – timing of scans may be difficult to negotiate, but standardize as much as possible. |

### Attribute of imaging BM
- Imaging devices, agents and software
- Imaging devices may not be designed, maintained or approved for the purpose of measuring the BM
- Innovation in imaging devices driven by competition to improve picture quality; has unpredictable effect on BM measurement
- Imaging contrast agent or tracer may not be designed, maintained or approved for the purpose of measuring the BM
- Non-proprietary software used for many imaging BM
- Resources and Staff
- Quality of the imaging BM data dependent on performance of radiologist and technician
- BM measurement dictated by workflow in Radiology and Nuclear Medicine departments rather than patient or oncologist needs

### Impact on technical validation
- Validation required for all sites
- Important factors affecting technical validation may be proprietary, obscure, and may change unexpectedly
- Validation required for all sites
- Withdrawal of agent in some markets, or failure to develop in certain markets severely limits availability
- Validation required for each software version

### Impact on biological validation
- None, if technical validation is performed correctly
- Important factors affecting technical validation may be proprietary, obscure, and may change unexpectedly
- Validation required for all sites
- May influence biological meaning for BM

### Impact on economic viability
- Unable to ensure most cost-effective BM acquisition (choices limited)
- Validation required for each software version
- May require patented software for translation across second ‘Cooksey’ translational gap
- Costs dictated by Radiology and Nuclear Medicine departments

### Biospecimen BM comparison
- Biospecimen BMs are analyzed using one (or a few identical) in vitro diagnostic devices
- Biospecimen BMs have stable platform due to regulatory approval
- Biospecimen BMs rarely require administration of a drug substance to the patient
- Pathology and Clinical Chemistry departments can accommodate patient and oncologist needs

### Imaging BM problems and solutions
- Many imaging BMs give numerically different values on different scanners.
- Parallel imaging changes noise characteristics and may affect measurement (e.g. ADC). Gradient improvements affect ADC.
- Examples of 'Sinerem', gadofosveset, and many PET tracers.
- Can hinder direct comparison between different centres. Central analysis hubs for multicentre studies. Use of phantoms to standardize. Need for CE style approval of software.
- Quality of lung/liver BMs may depend on control of motion. Some modalities are very user-dependent (e.g. ultrasound). Use highly trained staff, familiar with protocols.
- Ktrans vary with coffee – timing of scans may be difficult to negotiate, but standardize as much as possible.
Many imaging BMs can only be measured on new acquisitions (e.g. new tracer or new sequence is required) | Validation process must begin from scratch | Validation process must begin from scratch | Extremely costly | Validation from pre-banked samples is routine for most biospecimen BMs | May take many years to acquire enough new data for adequate statistical power
Set up and use Image-banks of clinical scan data where possible
Consortia are acquiring new data for validation (e.g. QuIC-ConCePT for \( K^{\text{trans}} \) and FDG biomarkers)
Perform multi-centre studies to speed up recruitment

### 3. Patient Requirements

| Patient commitment required | Takes up patient time | - | - | Less patient commitment required for biospecimen BMs | Patients may decline recruitment or may drop out of study
Careful patient selection

### 4. Tumour Sampling

| Imaging BMs are seldom defined analytes | Analytical accuracy is seldom a goal so alternatives must be devised | Biological validation seldom starts from underlying molecular biology ground truth
Need to agree compelling platform of evidence with all stakeholders | - | Biospecimen BMs usually related simply to a defined molecular entity via analytical biochemistry – this is often assumed in validation roadmaps | Imaging BMs may be difficult to relate to pathology
Research required to develop more appropriate pathology standards against which imaging is compared
Use of PFS/OS

Investigator has control over “sampling” of tumour/disease | Technical validation needs to be addressed separately for a) BM sampling part of lesion (e.g. \( \text{SUV}_{\text{max}} \)) b) BM sampling entire index lesion (e.g. mean \( K^{\text{trans}} \)) c) BM sampling multiple lesions (e.g. metastases) d) BM quantifying entire disease burden (e.g. whole body FDG or DWI) | Biological validation studies require careful comparison of imaging with single or multiple slice pathology specimens | Whole tumour approaches expected to be effective in capturing disease activity and response (e.g. PFS) | Tumour heterogeneity is a major confound
Biospecimen BMs suffer from confounds at either extremes: a) BM from part of lesion (e.g. biopsy) b) BM from all disease burden (e.g. circulating BM) | Spoilt for choice: must pick small number of primary endpoints that have technical and biological validation
Whole tumour coverage reduces sampling bias
ADC, \( K^{\text{trans}} \) heterogeneity BM may have benefit over average values (e.g. predict outcome)
Evaluate different biology in different lesions

### 5. BM Validation Landscape

| Little precedent for validation roadmaps in imaging BMs | Little consensus on what constitutes technical validation
Wildly divergent approaches between different funders, sponsors, and investigators | Little consensus on what constitutes biological validation
Wildly divergent approaches between different funders, sponsors, and investigators | Acquisition costs, analysis costs and study design make imaging studies expensive but must be addressed
Outcome studies may be prohibitively expensive, or impossible even in principle | Academic and regulatory roadmaps well-defined for biospecimen BMs
Biological validation on retrospective samples routinely used to construct Kaplan-Meier outcome plots | International consensus being sought from imaging community